

REMARKS**I. Status of the Claims**

Claims 1-14 are pending.

Claims 1 and 11 are amended.

Claims 1-7, 11 and 12 are under consideration, claims 8-10, 13-14 are withdrawn, but will be rejoined if composition claims are allowed.

II. Interview Summary

A telephone interview was held on Tuesday, August 26, 2008. Dr. Bernstein, the inventor, Alice Martin, applicant's representative, Examiner Kim, and Supervisor Padmanabhan were on the call.

Dr. Bernstein pointed out that this was a third interview in this prosecution history, the most recent, January 9, 2008, was followed up by a second Declaration showing additional results on effective pain relief due to a preponderance of cis over trans doxepin, without inducing sedation, a surprising advantage of the invention.

The current obstacles to obtaining a patent are one publication (Midha) cited in support of a rejection under 35 U.S.C. §103, and an allegation that "51%" as a substitute term in the claims for "preponderance" of cis, is new matter because "at least 51% cis lack literal support." There is no disagreement that the term "preponderance" is in the specification and original claims, or that compositions are enabled and shown to be operative, for over 50% cis. Applicant argued that support for 51% is due to established definitions of "preponderance" a term which is in the specification, and that the examiner provides no case law to support that literal (the number 51%) support is required.

Dr. Bernstein discussed that, contrary to the examiner's maintained position, Midha does **not** teach that cis is more active than trans. Midha's only reference to this is a background reference to Pinder et al. The record has already shown that Pinder is an animal study, not a clinical trial, and has conflicting results on the issue of whether cis doxepin is more active than trans.

Furthermore, even were cis more “active” than trans, this would be predicted to give more, not less sedation. The invention relates compositions that do **not** cause sedation. Furthermore, there is a teaching away from using cis to reduce sedation (see section III).

III. A Prima Facie Case of Obviousness is Not Established

Claims 1-7, 11-12 were rejected as obvious over Midha and applicant’s admission. The examiner did not contradict that the Midha reference merely cites to a publication by Pinder et al. in a sentence in Midha’s background, that the cis-isomer is more active than the trans isomer. (Office Action, page 4). This conclusion is not based on work by Midha, but is only supported by a cite to Pinder et al. [1] in the Background of Midha’s paper.

...although animal studies suggest that the cis-isomer may be the more active [1].

Pinder et al. – *Drugs* 13; 161-218 (1977)

In fact, Pinder reviews the confusing results of animal studies on doxepin effects, as illustrated by the following:

Pinder citation

- p166 cis more active than trans in antagonizing reserpine-induced hypothermia in mice (Schaumann & Rebbentrop 1966). Another study showed cis & trans have equivalent activity in the same model. (Otsuki et al 1972).
- p167 “Most of the activity of doxepin in this test appeared to reside in the *trans*-isomer, which comprises 85% of the commercially available drug; for the *cis* isomer was virtually ineffective.” Trans was much more active in inhibiting 5HT uptake. Cis virtually ineffective (Buczko et al 1974).
- p168 cis slightly more potent than trans at inhibiting avoidance behavior.
- p168 cis enhanced amphetamine-induced hyperactivity whereas trans antagonized the hyperactivity; cis more potent than trans in inhibiting conditioned avoidance behavior (Otsuki et al 1972b).
- p169 cis has greater anticholinergic effects than trans (Schumann & Ribbentrop 1965, 1966).
- p169 the cis isomer is more active in potentiating urethane-induced sedation (Schumann & Ribbentrop 1966), and cis is more potent than trans in hexobarbital-induced sleep in mice (Otsuki et al 1972).
- p170 cis more potent than trans in inhibiting acetylcholine-induced spasm in guinea pig ileum.

p171 cis & trans are **equivalent** in producing dose-related decrease in blood pressure in dogs.

(per Table 2 on p 250 of Ross) the cis is **more active** than the trans in some respects and **less active** than the trans in others.

Midha, the actual publication cited by the examiner, **only** teaches a composition 15% cis, 85% trans doxepin, which does not fall within the pending claims. Yet, as noted, U.S. 5,502,047 states that prior art doxepin compositions (predominantly trans isomer) can be used to treat insomnia. These two references, taken together, actually teach **away** from the instant invention, because they suggest that cis-doxepin would have a **greater** sedative effect, since it is more “active,” not a lesser effect as recited in the pending claims.

As promised during the interview of January 9, 2008, a Declaration under 37 CFR 1.132 was appended as Exhibit A to illustrate unexpected results with cis preponderant to trans.

The examiner argued that sedation effects are irrelevant in a composition claim, but applicant’s representative countered that even discounting an advantage of the composition over the standard 15% cis 85% trans composition according to Midha, the examiner cites to no publication teaching the composition as presently claimed. The art cited by the examiner (Midha) stated that 15% cis is standard. Dr. Bernstein’s claimed composition, a preponderance of cis, and all his examples, are a far cry from 15% cis. Therefore, a *prima facie* case of obviousness is not established -- the claim elements are **not** in the publication cited by the examiner.

“To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.” MPEP § 706.02(j) *quoting Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). A determination of obviousness requires that “the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.” *KSR International Co. v. Teleflex, Inc.*, -- U.S. --, 127 S.Ct. 1727, 1734, 82 U.S.P.Q.2d 1385 (2007) *quoting Graham v. John Deer Co.*, 383 U.S. 1, 17 (1966). In making a determination of obviousness by looking at the teachings of multiple patents, one should consider

the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an

apparent reason to combine the known elements in the fashion claimed by the patent at issue. *To facilitate review, this analysis should be made explicit.*

KSR, 127 S.Ct. at 1740-41 (*emphasis added*). “[A] patent composed of several elements is not proved obvious merely by demonstrating the each of its elements was, independently, known in the prior art.” *Id.* at 1741. In the present case, Midha does not even teach all the claimed elements.

IV. “51%” *cis* is Not an Issue

The established meaning of the word “preponderance” in the application includes “majority”, (see support in the record) so claims were previously amended to “at least 51% *cis*” to overcome this rejection, based on the interview of January 9, 2008. The examiner rejected this amendment as lacking support, so even though applicant disagrees, present claims are amended back to “preponderance” for which there is express support.

V. Conclusion

As all grounds of rejection have been overcome, a Notice of Allowance is respectfully requested. Applicants request allowance of the pending claims. No other fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (41959-102742).

Respectfully submitted,



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